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B406

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GB 1134878 A JP 86280435 A
Pharm. Res. 3(1), 48-51

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INT CL⁴ A61K

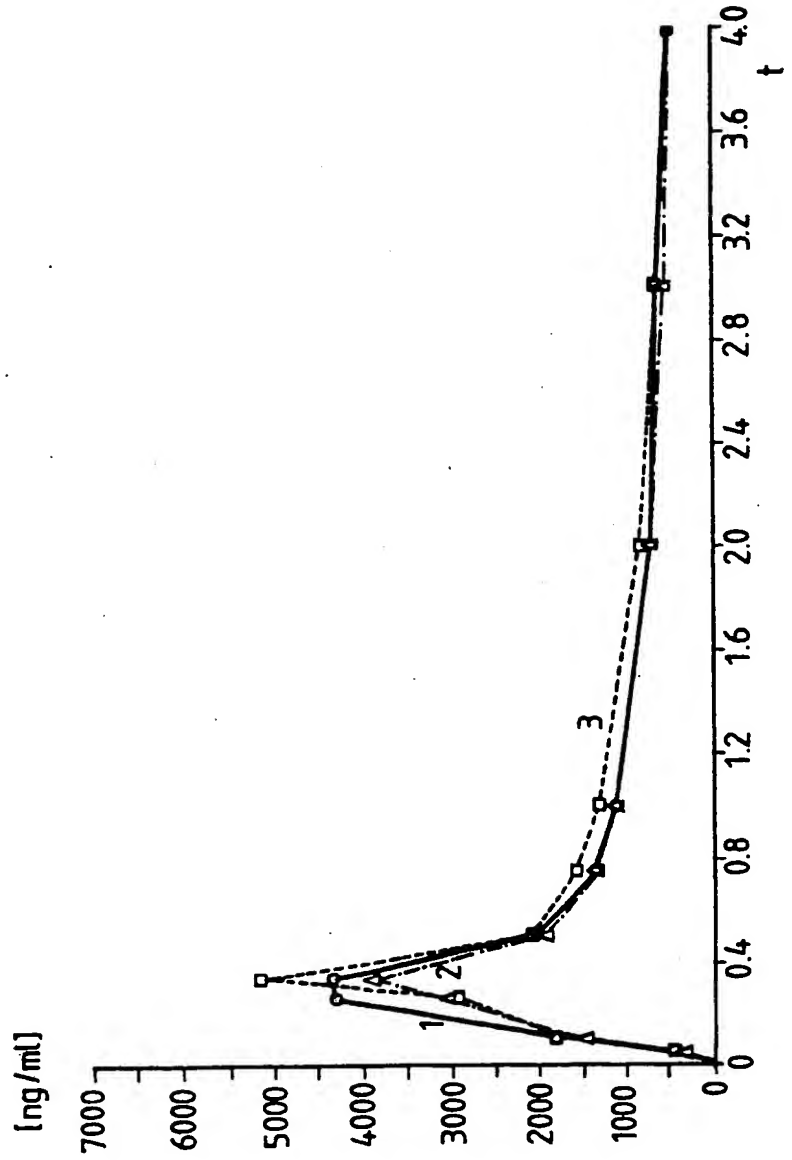
(54) Water soluble monoesters as solubilisers

(57) A combination of a pharmacologically active compound and a water soluble monoester of a saturated or unsaturated (C_{6-18}) fatty acid and a polyol, especially a saccharide, particularly as a solid solution of the active compound in the monoester.

The solid solution is especially suitable for substantially water insoluble active compounds, particularly such polypeptides, e.g. cyclosporins and is in all desirable weight ratios miscible with water.

GB 2 209 671 A

FIG. 1


[ng/ml]
7000
6000
5000
4000
3000
2000
1000
0
0.4
0.8
1.2
1.6
2.0
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3.2
3.6
4.0
t
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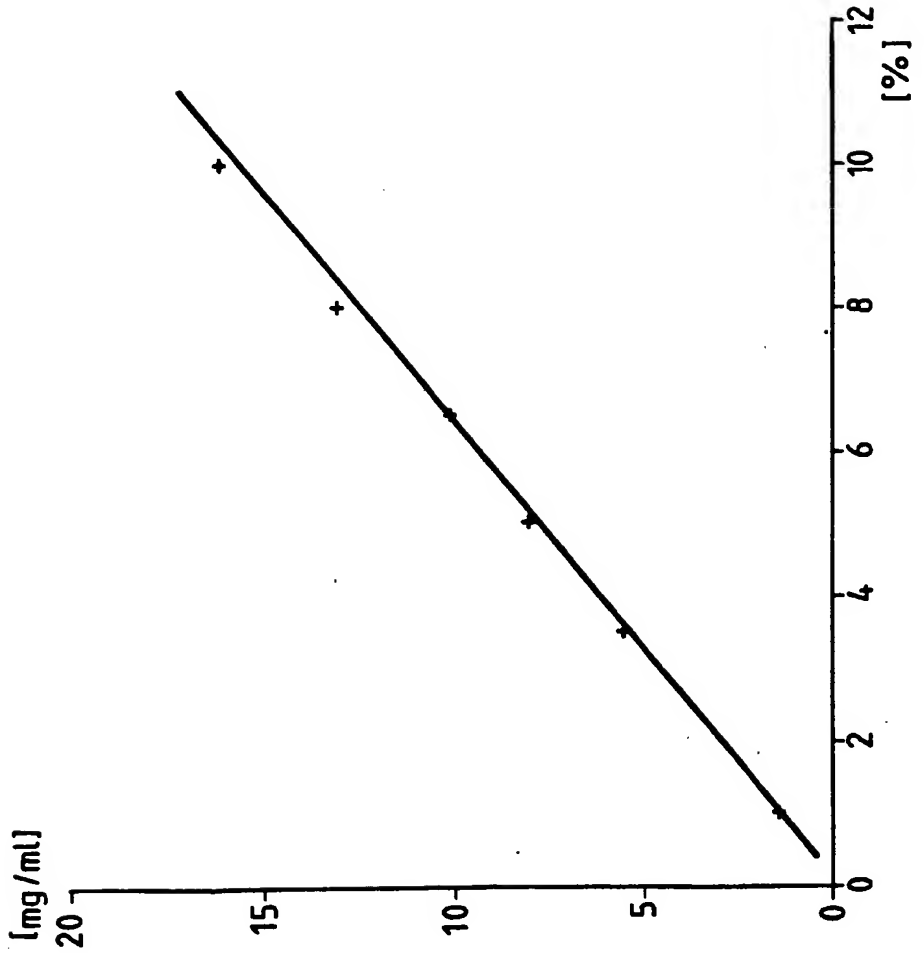
2
3

FIG. 2



2209671

CASE 100-7207

WATER SOLUBLE MONOESTERS AS SOLUBILISERS FOR PHARMACOLOGICALLY ACTIVE COMPOUNDS AND PHARMACEUTICAL EXCIPIENTS

The invention relates to the use of water soluble monoesters of saturated or unsaturated (C_{6-18}) fatty acids and polyols, preferably saccharides, as solubilisers of pharmaceutically active compounds in intravenously applicable solutions in aqueous media or in solvents which are miscible with water, e.g. polyethylene glycol, ethanol, glycerin or 1,2-propylene glycol.

[By the term "water soluble" as used herein is meant: having a solubility in water of at least 3.3 % at room temperature. Water soluble monoesters as herein defined are thus monoesters dissolvable in water at room temperature in an amount of at least 1 g monoester per 30 ml water.

The term "aqueous medium" is to be understood to include systems comprising a liquid phase comprised entirely or substantially entirely of water, as well as systems in which the liquid phase additionally includes or comprises water miscible solvents such as hereinabove set forth. Preferred aqueous media are such in which the liquid phase comprises at least 75 %, preferably at least 90 %, most especially at least 95 % water by weight.]

The invention provides a combination of such a monoester and a substantially water insoluble pharmaceutically active polypeptide, particularly a cyclopeptide, preferably a cyclosporin.

[By the term "substantially water insoluble" is meant: having a solubility in water of not more than 1 % at room temperature. Substantially water insoluble polypeptides as defined above are thus polypeptides requiring at least 100 ml water to effect dissolution of 1 g thereof at room temperature. Preferably the term is applied to substances, e.g. polypeptides having a solubility in water of not more than 0.1 %, in particular not more than 0.01 %, e.g. not more than ca. 0.004 % at room temperature.]

The mentioned monoesters are generally known. From UK-Patent 1.134.878 it is also known, to use water soluble raffinose monoesters of the same category as solubilisers to stabilise specified non polypeptide agents, e.g. the triterpenealcoholester of 3-methoxy-4-hydroxycinnamic acid in solutions for injection or for oral application. However, and this is an important feature, considerable amounts of several other excipients (cosolubilisers) were necessary to guarantee a satisfactory stable solution (cf. page 5, lines 2-18). Hence, it follows, that for the used agent the applied monoesters alone were not satisfactory solubilisers. Additionally it appeared that the saccharose monoesters were not suitable as solubilisers at all for the used agent (cf. page 2, lines 70-73). The products obtained are indicated for e.g. intradermal injection but not as suitable for intravenous injection (page 8, column 2, lines 3-4). Surprisingly liquid preparations according to the present invention are suitable for intravenous injection.

UK-Patent 2.126.588 relates to the stabilisation of, e.g. injectable, liquids containing tumor necrosis factor (TNF) against decomposition of the active substance employing a wide variety of non-ionic solubilisers (esters and ethers). In the examples many polyoxyethylene derivatives are discussed including inter al. sorbitan monopalmitate and sorbitan

oleate. Most solubilisers are not water soluble themselves and thus not intravenously injectable. In particular the sorbitan esters are not water soluble as herein defined. Again co-solubilisers must be used (cf. page 3, lines 16-22). According to the instant invention no such excipients are neccessary.

Saccharose fatty acid esters are also mentioned in the description (not in the examples) incidentally and only the monopalmitic and the monostearic acid esters are specified (page 4, line 11). These compounds too do not meet the requirement of the instant invention, that should they be water soluble. No suggestion can be found to use water soluble monoesters for the improvement of the water solubility of pharmaceutically active polypeptides.

UK-Patent 1.601.613 discloses mixtures of non-ionic solubilisers, among others saccharose monoesters generally (page 2, line 53) and saccharose monopalmitate specifically (page 2, line 53), and agents, e.g. proteins or insulin (page 2, line 24). The indicated solubilisers (the saccharose monopalmitate is not water soluble) are used for the improvement of the resorption of agents, which are badly resorbable after oral application. There is no teaching to use the esters as solubilisers for the production of aqueous solutions, since the agents already have relatively good water solubility by nature (cf. page 1, lines 17-21 and page 2, lines 19-20). The obtained aqueous mixtures are not solutions (page 1, lines 33-39), but dispersions (page 2, line 3 and page 2, lines 63-page 3, line 4) and are recommended for rectal and not for intravenous application.

Japanese patent application no. 86 280 435 relates to the preparation of aqueous dispersions of cyclosporins for oral use. Monoesters which are applied are mostly not water soluble solubilisers, e.g. saccharose monopalmitate, saccharose monostearate or a sorbitan fatty acid ester. Saccharose monooleate was also used, but it was not found that this ester gives a clear solution.

In one of the examples a dispersion of a saccharose mono fatty acid ester and Ciclosporine is sonicated, to provide an oral liquid preparation. No indication can be found to use the obtained dispersion for intraveneous administration. For a dispersion containing 0.35% of Ciclosporine in water (3,5 mg/ml) a concentration of 0.2% monoester is employed. According to the instant invention solutions comprising 0.35% of Ciclosporine by weight are obtainable using a 2.3% solution of the water soluble saccharose monolaurate in water.

The present invention also provides compositions, in particular pharmaceutical compositions, comprising combinations of saccharose monolaurate or raffinose monolaurate with polypeptides. Such compositions may optionally include pharmaceutical excipients, which are substantially insoluble in water. Such excipients include e.g. benzene derivatives, e.g. p-hydroxybenzoic acid methyl ester.

The invention also provides solid solutions comprising pharmaceutically active, particularly substantially water insoluble pharmaceutically active compounds in the said water soluble monoesters.

Pharmaceutically active, substantially water insoluble compounds often suffer from a loss of bioavailability if applied orally. This is because they are insufficiently rapidly dissolved in the aqueous medium of the gastro-intestinal tract and are eliminated from the body, in substantial amount in undissolved form.

It is difficult to find water soluble excipients, which solubilise the pharmaceutically active compounds in aqueous media to provide solutions which are stable at all dilution stages without forming a precipitate, and which are additionally pharmaceutically acceptable. Liquid galenical forms, which are satisfactory from a pharmaceutical and medical viewpoint and which contain, in particular, substantially water insoluble polypeptides, especially cyclopeptides such as the cyclosporins, have long been sought. Excipients used in available commercial forms possess

poor palatability or are associated with a risk of anaphylactic shock. Tensides containing ethylene oxide units or such having amine or amide structures are no longer acceptable from a pharmaceutical or medical viewpoint.

Surprisingly, it has now been found that in this respect unobjectionable water soluble monoesters of saturated or unsaturated (C_{6-18}) fatty acids and polyols, especially saccharides, are extremely well suited solubilisers, especially for pharmaceutically active, substantially water insoluble compounds. It has further been observed, that the said monoesters form solid solutions with pharmaceutically active compounds. These monoesters can dissolve the active compound sufficiently. By addition of water or other aqueous media, aqueous micellar solutions are obtained from which the active compound is readily bioavailable. The active compound is completely solubilized in the colloidal solution.

The invention in particular provides solid solutions comprising polypeptide agents, particularly substantially water insoluble polypeptide agents in water soluble monoesters of saturated or unsaturated (C_{6-18}) fatty acids and polyols, especially saccharides. The fatty acid residues in the said esters may be substituted e.g. by hydroxyl.

Hydrotropic substances or cosolubilisers are not essential in the solid solutions of the invention. The used solubilisers do not contain ethylene oxide, amine or amide structural units, which are pharmaceutically or medically objectionable.

In accordance with the present invention solid solutions are obtainable in which the pharmaceutically active, e.g. substantially water insoluble, pharmaceutically active agent, e.g. polypeptide, for example cyclosporin (i.e. the dissolved or disperse phase) is entirely or substantially entirely present in molecular distribution, or in which the water soluble fatty acid ester (i.e. the solvent or continuous phase) and the water insoluble pharmaceutically active agent are each in entirely r substantially

entirely amorphous state, e.g. as verifiable by X-ray structure analysis. Solid solutions meeting the above criteria are preferred.

The water soluble fatty acid esters employed in the compositions of the invention are themselves pharmaceutically acceptable.

Preferred fatty acid esters for use in practicing the invention are monoesters of disaccharides, e.g. maltose, or, especially, saccharose, as well as of trisaccharides, e.g. raffinose. Preferred are saccharides which contain glucose, fructose and/or galactose units.

The fatty acid esters for use in practicing the invention are preferably caproic acid (C_6), caprylic acid (C_8), capric acid (C_{10}), lauric acid (C_{12}), myristic acid (C_{14}), palmitic acid (C_{16}), oleic acid (C_{18}), ricinoleic acid (C_{18}) or 12-hydroxystearic acid (C_{18}) esters.

In the fatty acid esters used in practicing the invention the lipophilicity of the acid moiety is, by the choice of its length, in balance with the hydrophilicity of the polyol, e.g. saccharide, moiety. Preferably (C_{6-14}) acid residues are connected with disaccharides and (C_{8-18}) acid residues with trisaccharides.

In general the HLB-value of the fatty acid ester is preferably at least 10. Suitable fatty acid esters are in particular saccharose monocaproate, saccharose monolaurate, saccharose monomyristate, saccharose monooleate and saccharose monoricinoleate, raffinose monocaproate, raffinose monolaurate, raffinose monomyristate, raffinose monopalmitate and raffinose monooleate. Saccharose monolaurate and raffinose monolaurate are especially preferred.

The monoester content of fatty acid esters used in practicing the invention is preferably at least 80 %, more preferably at least 90 % by weight, i.e. the said fatty acid esters preferably contain less than 20 %, more preferably less than 10 % f di- or poly-ester impurities. The esters can

be produced in a manner known per se, e.g. as described in the Journal of the Society of Cosmetic Chemists (1956) 7 249-255 and are preferably purified by column chromatography in order to obtain a maximal monoester content.

Pharmaceutically active compounds comprised in the solid solutions of the invention are water soluble or, preferably, substantially water insoluble, e.g. Proquazone (= 1-isopropyl-7-methyl-4-phenyl-2(1H)-quinazolinone) which has a water solubility of below 0.1 g/100 ml; xanthine derivatives, e.g. theophyllin; tricyclic compounds, for example tricyclic antidepressiva or e.g. ketotifen; azulene derivatives, e.g. guajazulene, or steroids, e.g. Prednisone.

Water soluble pharmaceutically active compounds are included in the invention of the solid solution, since such agents are as advantageous as substantially water insoluble agents in combination with water soluble monoesters, since their bioavailability becomes improved.

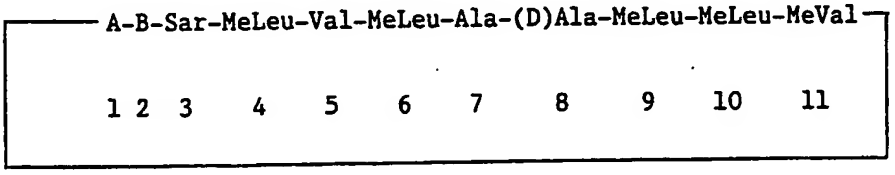
Preferred pharmaceutically active compounds in the mixtures, as well as in the solid solutions of the invention, are polypeptides, especially substantially water insoluble polypeptides having a molecular weight of from 500 to 10'000, e.g. of from 500 to 1'500.

To this class of compounds especially belong the cyclopeptides, e.g. the cyclosporins, particularly Ciclosporine, which has a water solubility of below 0.004 g/100 ml.

The cyclosporins comprise a class of structurally distinct cyclic, poly-N-methylated undecapeptides having valuable pharmaceutical, in particular immunosuppressive, anti-inflammatory and anti-parasitic, in particular anti-protozoal activity. The first of the cyclosporins to be isolated and the "parent" compound of the class, is the naturally occurring fungal metabolite Ciclosporine, also known as Cyclosporin A, the production and properties of which are described e.g. in US Patent No. 4,117,118.

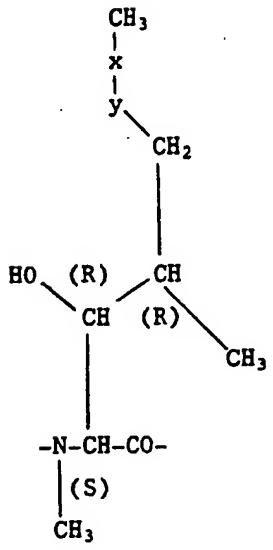
Since the original discovery of Ciclosporine a wide variety of naturally occurring cyclosporins have been isolated and identified and many further non-natural cyclosporins have been prepared by synthetic or semi-synthetic means or by the application of modified culture techniques. The class comprised by the cyclosporins is thus now substantial and includes, for example, the naturally occurring cyclosporins (Thr^2)-, (Val^2)- and (Nva^2)- Ciclosporine (also known as cyclosporins C, D and G respectively), as well as various semi-synthetic derivatives thereof, such as their dihydro derivatives (e.g. as disclosed in US Patents Nos. 4,108,985; 4,210,581 and 4,220,641) including e.g. (Dihydro-$MeBmt^1$)-(Val^2)-Ciclosporine (also known as dihydrocyclosporin D) and other natural and artificial cyclosporins such as those disclosed in European Patent Publication No. 0,058,134 B1, for example [(D)-Ser^8]-Ciclosporine; UK Patent Application No. 2,115,936 A, for example [O-Acetyl-(D)-Ser^8]-Ciclosporine; and European Patent Application No. 86810112.2, for example [Val]^2-[(D)Methylthio-Ser]^3- and [Dihydro-MeBmt]^1-[Val]^2-[(D)-Methylthio-Sar]^3-Ciclosporine.

[In accordance with now conventional nomenclature for the cyclosporins, these are definded herein by reference to the structure of Ciclosporine (i.e. Cyclosporin A). This is done by first indicating those residues in the molecule which differ from those present in Ciclosporine and then Applying the term "Ciclosporine" to characterise the remaining residues which are identical to those present in Ciclosporine. Ciclosporine has the formula I



(I)

wherein A represents the [N-methyl-(4R)-4-but-2E-en-1-yl-4-methyl-(L)-threonyl] residue of formula II



(II)

in which -x-y- is -CH=CH- (trans), which residue is abbreviated as -MeBmt-, and
B is the alpha-aminobutyric acid residue, abbreviated as -αAbu-.
Accordingly (Thr^2)-Ciclosporine (cyclosporin C) is the compound of formula I, wherein A has the meaning given above and B is -Thr-, and ($Dihydro\text{-}MeBmt^1$)-(Val^2)-Ciclosporine (dihydrocyclosporin D) is the compound of formula I, wherein A represents the -dihydro-MeBmt- residue of formula II above in which [x-y- is $-CH_2-CH_2-$, and B is -Val-].

As the "parent" compound of the class, Ciclosporine has so far received the most attention. The primary area of clinical investigation for Ciclosporine has been as an immunosuppressive agent, in particular in relation to its application to recipients of organ transplants, e.g. heart, lung, combined heart-lung, liver, kidney, pancreatic, bone marrow,

skin and corneal transplants and, in particular, allogenic organ transplants. In this field Ciclosporine has achieved a remarkable success and reputation and is now commercially available and widely employed in clinic.

At the same time, applicability of Ciclosporine to various autoimmune diseases and to inflammatory conditions, in particular inflammatory conditions with an aetiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases, has been intensive and reports and results in vitro, in animal models and in clinical trials are wide-spread in the literature. Specific autoimmune diseases for which Ciclosporine therapy has been proposed or applied include autoimmune hematological disorders (including, e.g. hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopaenia), systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis and Crohn's disease) endocrine opthalmopathy, Graves disease, sarcoidosis, multiple sclerosis, primary billiary cirrhosis, primary juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), conjunctivitis (e.g. keratoconjunctivitis for example, vernal keratoconjunctivitis and keratoconjunctivitis sicca), interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy).

A further area of investigation has been potential applicability as an anti-parasitic, in particular anti-protozoal agent, with possible uses suggested including treatment of malaria, coccidiomycosis and schistosomiasis.

Other cyclosporins exhibit equivalent pharmacological utility as Ciclosporine and various proposals for application, in indications, as set forth above are prevelant in the literature.

Dosaging for Ciclosporine (which is commerciable available under the Registered Trade mark SANDIMMUN) varies considerably from subject to subject and with condition to be treated, as well as with the course of therapy and use of concommitant therapy. In general, dosaging is monitored by HPLC, RIA or equivalent assay of blood levels and individual subject dosaging is adjusted to maintain desired serum levels. Commonly, oral dosaging starts at 10 or 15-20 mg/kg day for initating therapy, reducing to 3/5 - 10 mg/kg day. Intravenous infusion is at ca. 3-5 mg/kg day for initiating therapy reducing to ca. 2-3 mg/kg day for maintenance therapy (where infusion is required, e.g. in the case of rejection crisis).

Solid solutions in accordance with the present invention preferably comprise at least 7%, particularly at least 10% by weight of pharmaceutically active, substantially water insoluble pharmaceutically active, compound.

Solid solution in accordance with the invention comprising a cyclosporin as active ingredient preferably comprise up to 30% of weight of cyclosporin based on the total weight of ester plus cyclosporin. Lowest concentration is only determined in relation to the therapy to be applied but should not be below 1% by weight.

Solid solutions comprising a cyclosporin in saccharose monolaurate or in raffinose monolaurate are preferred. In the first - pure - monoester solid solutions containing up to 16%, in the second monoester solutions up to 13,5% cyclosporin are preferred since they can be diluted with water without forming a cyclosporin precipitate. It is generally preferred to use as high a concentration as possible.

The solid solutions of the invention may be employed as, or as components of, pharmaceutical compositions. In a further aspect the present invention thus also provides: a pharmaceutical composition comprising a solid solution as herein described or defined.

Such pharmaceutical compositions include dosage forms suitable for direct administration, for example unit dosage forms for oral administration, for example tablets, capsules or the like comprising or containing a solid solution in accordance with the invention. Such compositions can be prepared in accordance with conventional techniques, e.g. by appropriate forming of the solid solution or by grinding or milling of the solid solution and compounding of the obtained particulate, e.g. fine particulate, product, optionally together with other ingredients, e.g. fillers, carriers, diluents and so forth, for tabletting or for filling into capsule shells.

The solid solutions of the invention may equally be employed in the manufacture of other conventional solid dosage forms, e.g. oral dosage forms such as pellets and granulates, topical dosage forms such as creams, gels, ointments and the like, e.g. for application to the skin or eye; and rectal dosage forms such as suppositories.

Oral unit dosage forms as aforesaid comprising a cyclosporin as active ingredient, for example Ciclosporine, suitably comprise from 20 to 250, preferably 25 to 100, e.g. about 50 mg cyclosporin per unit dosage. Suitably the ratio of water soluble fatty acid ester to cyclosporin in such compositions is of the order of from 10:0.5 to 10:3.0, especially from 10:1.0 to 10:2.0, e.g. about 10:1.2 to 10:1.6 parts by weight.

Such pharmaceutical compositions also include dosage forms intended for dilution in aqueous media prior to administration, for example infusion concentrates comprising or consisting of said solid solutions, to be dissolved in an appropriate aqueous infusion medium such as physiological saline, for administration i.v., as well as preparations for disso-

lution in aqueous media, e.g. drink preparations and the like, prior to ingestion. To aid dissolution, such compositions will preferably comprise the solid solution in particulate, especially fine particulate, form, optionally together with other excipents or additives. Where such compositions comprise a cyclosporin as active ingredient the ratio of ester to ciclosporin will appropriately be as described above in relation to unit oral dosage forms.

Compositions of this type will conveniently be presented in an appropriate container e.g. ampoule, phial bottle or the like.

The solid solutions of the invention are readily soluble in aqueous media to provide solutions which may be further diluted to any desired concentration without clouding or precipitation. At high concentrations increase in viscosity is observed. On further dilution clear micellar solutions are formed. Such solutions are also novel and form part of the invention.

More particularly the invention provides: a solution obtained by dissolving a solid solution as herein described or defined in an aqueous medium or in a solvent which is miscible with water;
as well as: a solution comprising a substantially water insoluble, pharmaceutically active polypeptide and a water soluble monoester of saturated or unsaturated (C_{6-18}) fatty acid and a polyol (as solubiliser for said peptide) in an aqueous medium or in a solvent which is miscible with water.

If such a liquid solution is formed by simultaneous mixing of the three components monoester, active compound and water, a liquid solution of active compound, especially in higher concentration, is only possible after vigorous agitation. For this reason, the most simple method is, firstly preparing the solid active compound solution in the monoester, after which diluting with water can be carried out without problems. Dissolving the active compound in the liquified monoester and subsequently diluting the obtained mixture, after an optional intermediate

treatment with hot ethanol, with water is known from the GB-Patent 1.134.878 (page 3, lines 22-32 and page 6, lines 34-39). However, there is no teaching, that an intermediate cooling is practised and that a solid solution would have been formed.

Liquid solutions of the invention are clear or perfect or substantially clear or perfect. The pharmaceutically active component, e.g. substantially water insoluble peptide component is preferably present entirely or substantially entirely in true solution. Solutions of the invention are free or substantially free of pharmaceutically active component in colloidal or other associated or particulate form. They are free or substantially free of turbidity or clouding as may be evidenced by freedom from formation of precipitate or deposit on ultracentrifugation.

Solutions in accordance with the invention in aqueous media may of course comprise or be present together with further components other than water. They may for example also incorporate water miscible components. Such solutions equally include solutions as defined in which other non water soluble, e.g. colloidal components are present, e.g. in dispersion, for example, in the case of solutions for oral administration, flavouring agents and so forth. For the purposes of i.v. administration solutions in accordance with the invention will preferably comprise the active ingredient and the fatty acid component in an intravenously administrable aqueous medium such as isotonic saline and be free or substantially free of water insoluble additives. Liquid solutions in accordance with the invention may also be employed as or as components of occular formulations, e.g. eye drops.

The present invention accordingly also provides: a pharmaceutical composition (for example for intravenous, oral or occular administration) comprising a solution in an aqueous medium as herein described or defined.

The invention also provides using the liquid solubilisate solution as well as the solid solution orally, buccally, lingually, occularly, cutaneously, intracutaneously, percutaneously, vaginally or rectally. The solubilisate solution can additionally be applied parenterally.

Solid solutions of Ciclosporine in accordance with the present invention and aqueous solutions derived from the use are usable as alternative for the existing intravenous Ciclosporine infusion concentrate in alcohol in the presence of Cremophor^{R} EL, a polyoxyethylated castor oil, or the oral solution in olive oil, which are the state of the art for Ciclosporine.

A comparison of Ciclosporine and saccharose or raffinose monolaurate containing aqueous solutions of the invention with the mentioned Cremophor^{R} EL containing Ciclosporine infusion concentrate in a test in which dogs were injected intravenously with these solutions, did not show different Ciclosporine plasma concentrations. This means that the distribution of the active compound in the body is the same. In Figure 1 the concentrations are plotted in ng/ml and the time t in hours. Curve 1 presents the saccharose monolaurate solution, curve 2 the raffinose monolaurate solution and curve 3 the commercial solution.

A comparison of a saccharose monolaurate containing Ciclosporine solution with the commercial solution in olive oil in a test in which these solutions were administered orally to rats resulted in a bioavailability improvement of 26% of the solution according to the invention.

The invention also provides a solid solution of a water soluble pharmaceutically active compound in a monoester, used according to the invention, since an improvement of bioavailability is also obtained with this type of agent.

The production of the solid solution is preferably carried out in such manner, that the agent and the sugar ester are dissolved together in a liquid solvent and the solvent is volatilised from the obtained mixture.

Volatilising can be realised by evaporation or by freeze drying. As a volatile solvent water or preferably ethanol are used. If water is used, volatilising is preferably effected by freeze drying. The invention also provides a process for the production of the solid solution, comprising dissolving the active compound and the monoester together in a volatile solvent, volatilising the solvent and recovering the obtained solid solution.

The invention additionally provides a process comprising melting the monoester by heating, dissolving the active compound in the melt, solidifying by cooling and recovering the obtained solid solution. Additional pharmaceutical excipients can be added to the solid solution, e.g. to lubricate, to thicken or to dye it. Excipients which are substantially water insoluble are solubilised under the influence of the monoester and can also be incorporated in the solid solution.

Especially when the solid solution is obtained according to the firstly described process, an anti-microbiological treatment is possible before the solid solution is formed and filled in ampoules. The anti-microbiological treatment can be easily integrated in the process of production, if the solid solution is formed according to the secondly described process by raising the liquefaction temperature.

The weight ratios of the amount of active compound to the amount of monoester can be varied up to the maximum solubilisation capacity of the monoester.

The saccharose ester of lauric acid is an excipient, widely distributed in the food industry and is easily biodegradable. The solubilisation capacity of the monoester, having a mono ester content of >80%, for Ciclosporine in aqueous solutions at room temperature and at different monoester concentrations was as follows:

TABLE I

Saccharose monolaurate concentration in water, containing 0.9% of weight of NaCl.	Solubilising capacity for Ciclosporine in mg/ml at room temperature.
1 %	1,5 mg/ml
3,5	5,5
5	8,0
6,5	10,0
8	13,0
10	16,0
20	35,0

The solubilising capacity in mg/ml and the concentration of the solubilisator solution in % of weight are plotted in Fig. 2; a constant ratio is shown. The Ciclosporine solid solution can thus be diluted with the brine to every desirable extent, without destabilisation and precipitation of the drug compound or the solution becoming opalescent.

From table 1 it is seen that a maximum concentrated aqueous solution of Ciclosporine can be obtained if the weight ratio of the monoester to Ciclosporine is 100:16.

The present invention yet further provides a solid solution or solution in an aqueous medium as hereinbefore defined or described, for use as a pharmaceutical; as well as a method for effecting therapy employing a pharmaceutically active substance in a subject requiring treatment with said substance, which method comprises administering a solid solution or solution in an aqueous medium as herein defined or described and comprising said substance as active ingredient, in an amount sufficient to effect therapy.

As applied to the solid solutions of the invention and solutions of the invention in aqueous media comprising a cyclosporin as active ingredient the present invention accordingly provides:

a) use thereof as immunosuppressants, for the treatment of inflammatory conditions or for the treatment of parasitic disease, e.g. use in any of the diseases or conditions hereinbefore described in relation to cyclosporin, e.g. Ciclosporine, therapy, as well as

b) methods of immunosuppressive, anti-inflammatory or anti-parasitic treatment, e.g. methods of treatment of any of the specific diseases or conditions hereinbefore described in relation to cyclosporin, e.g. Ciclosporine, therapy, comprising use thereof in immunosuppressive, anti-inflammatory or anti-parasitic effective amounts.

As will be apppreciated, all components of solid solutions and solutions in aqueous media for use as defined above will themselves be pharmaceutically acceptable, e.g., in relation to intravenous administration, intravenously applicable.

The following examples are illustrative of the present invention:

A) Preparation of solid solution and their use

Example 1

A suitable saccharose monolaurate is, since it has a monoester weight content of >80%, the commercially available product L-1695 of Mitsubishi--Kasei Food Corporation, Tokyo 104, Japan. The product has an HLB-value of at least 12.3. The purity of the lauryl ester residue is about 95%. The melting point is about 35°C, the decomposition temperature is about 235°C. The surface tension of an aqueous solution containing an amount of 0.1% of weight of monoester is about 72.0 dyn/cm at 25°C.

1000 mg of this saccharose monolaurate product and 160 mg of Ciclosporine are dissolved in 20ml of ethanol and the solvent evaporated in a Rotavaporisator to yield the desired solid solution.. The residue is pulverised in a mortar under dry conditions, since the monoester is hygroscopic.

Example 2

1000 mg of the saccharose monolaurate of Example 1 are mixed with 160 mg of Ciclosporine and the mixture heated to 150°C while stirring. The obtained clear solution is cooled to room temperature to yield the desired solid solution and then processed further as described in Example 1.

Example 3

a) 1000 mg of the saccharose monolaurate employed in Example 1 and 30 mg of Proquazone (Biarison^{R}) are dissolved in 20ml of 100 % ethanol and the solvent evaporated completely in a Rotavaporisator to yield the desired solid solution. The residue is reduced to a fine powder in a mortar and is mixed with 10 mg of magnesium stearate as a lubricator.

b) A similar solid solution is obtained by substituting the Proquazone ingredient with 30 mg of Progesterone.

Example 4

Solid solutions having the following compositions are obtainable analogously to Example 1.

SOLID SOLUTION	CICLOSPORINE CONTENT	SACCHAROSE MONOESTER CONTENT *
A	120 mg	1000 mg Saccharose monocaproate
B	130 mg	1000 mg Saccharose monomyristate
C	250 mg	1500mg Saccharose monooleate

*Monoester content for all listed esters >80 %.

The obtained solid solutions are completely soluble in water.

Example 5

Solid solutions containing Ciclosporine in 1000 mg of raffinose monolaurate and in 1000 mg of raffinose monooleate respectively (monoester content >80%) are prepared using the evaporation method. In the raffinose monolaurate 135 mg of Ciclosporine and in raffinose monooleate 200 mg of Ciclosporine could be dissolved. The obtained solid solutions are completely soluble in water.

Example 6

2000 mg of saccharose monolaurate (monoester content >80%) and 320 mg of Ciclosporine are dissolved in 50 ml of an aqueous solution containing 10% of weight of ethanol and the liquid micellar solution is filled in ampoules for injection and lyophilised under sterile conditions. The thus obtained solid solution in the ampoule can be dissolved within 30 seconds by shaking in a 0.9% NaCl containing aqueous solution to yield a clear solution as product.

EXAMPLE 7

362 mg of a solid solution prepared according to the method of Example 1 are mixed with 375 mg of water free citric acid and 150mg of sodium bicarbonate and the mixture pressed. The thus obtained effervescent tablet contains 50mg of Ciclosporine and dissolves within 2.5 minutes in water without leaving a residue. The obtained solution is adminsterable orally to provide effective Ciclosporine therapy, e.g. on administration of one or several such dosages, e.g. 2 to 4x per day.

Example 8

181.25 mg of a solid solution, prepared according to the method of Example 1 containing 25 mg of Ciclosporine are mixed while stirring with 198.75 mg of viscous liquid paraffin and filled into hard gelatine capsules. The release rate of Ciclosporine from the obtained oral unit dosage form is measured in water at 37°C:

Time (min.)	% of weight of Ciclosporine dissolved mean value (n=3)	standard deviation
5	3	2,2
10	14	3,5
15	29	6,8
30	65	7,0
60	98	0,6
120	98	0,6
180	98	0,6

Example 9

1000 mg of saccharose monolaurate (monoester content >80%) and 30 mg of Proquazone (Biarison^{R}) are processed according to the evaporation method to a solid solution. The powder is moulded with 1.0 g of Adeps solidus Ph. Eur. to a suppository, thus diminishing the hygroscopicity.

B) Preparation of a liquid micellar solution and its use

For human application the solid solution is preferably transformed into a liquid (aqueous) micellar solution, of which generally a dosis is used corresponding to an amount of 40 to 2000 mg of Ciclosporine for oral or intravenous application. For the oral application the higher dosage and for intravenous application the lower dosage within the range are taken.

Example 10

16 mg of Ciclosporine are solubilised in 1 ml of an isotonic aqueous solution of 10% of weight of saccharose monolaurate with a monoester amount of >80% of weight. The solution is used for the treatment of Psoriasis by intralesional injection. Repeated injection is effective in the treatment of Psoriasis.

Example 11

1000 mg of saccharose monolaurate having a monoester content of >80% by weight and 160 mg of Ciclosporine are dissolved in a liquid mixture of 16 ml of 1,2-propylene glycol and 91 ml of distilled water, sterilised by filtration and filled in an ampoule for injection. The dosage of 1.5 mg of Ciclosporine pro ml of solubilisate solution corresponds to the average dosage range and a dilution to a ratio of 1:33 of the normal Ciclosporine infusion concentrate of 50 mg/ml.

Example 12

With p-hydroxy benzoic acid methyl ester as a substantially water insoluble excipient, Proquazone (Biarison^{R}) and Progesterone as substantially water insoluble pharmaceutically active compounds, clear solubilisate solutions are prepared with saccharose monolaurate having a monoester content of >80%. In an aqueous solution of solubilisate (10% by weight) 8 mg of p-hydroxybenzoic acid methyl ester, 3 mg of Proquazone and 3 mg of Progesterone can be solubilised per ml. The solubilisate solutions are stable over a long period of time at room temperature. A solid solution is obtained by removing the water by freeze drying.

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CLAIMS

1. A water soluble monoester of a saturated or unsaturated (C_{6-18}) fatty acid and a polyol for use as a solubiliser of a substantially water insoluble pharmaceutically active polypeptide in intravenously administrable clear solutions in an aqueous medium or in a solvent, which is miscible with water.

2. A mixture of a water soluble monoester of a saturated or unsaturated (C_{6-18}) fatty acid and a polyol and a substantially water insoluble pharmaceutically active polypeptide, which comprises saccharose monolaurate or raffinose monolaurate as the monoester.

3. A mixture according to claim 2 of a water soluble monoester and a cyclosporin.

4. A pharmaceutical composition comprising saccharose monolaurate or raffinose monolaurate and a substantially water insoluble pharmaceutically active polypeptide and optionally a subtantially water insoluble excipient.

5. A solid solution comprising (a) a pharmaceutically active compound and (b) a water soluble monoester of a saturated or unsaturated (C_{6-18}) fatty acid and a polyol.

6. A solid solution according to claim 5 wherein (b) comprises a water soluble monoester of a saturated or unsaturated (C_{6-18}) fatty acid and a saccharide.

7. A solid solution according to claim 6 wherein (b) comprises a monoester of a disaccharide.

8. A solid solution according to claim 7 wherein (b) comprises a monoester of saccharose.

9. A solid solution according to claim 6 wherein (b) comprises a monoester of a trisaccharide.

10. A solid solution according to claim 9 wherein (b) comprises a monoester of raffinose.

11. A solid solution according to claim 6 wherein (b) comprises a monoester of a saccharide containing a glucose unit.

12. A solid solution according to claim 6 wherein (b) comprises a monoester of a saccharide containing a fructose unit.

13. A solid solution according to claim 6 wherein (b) comprises a monoester of a saccharide containing a galactose unit.

14. A solid solution according to claim 5 wherein (b) comprises a monoester of caproic acid (C_6), caprylic acid (C_8), capric acid (C_{10}), lauric acid (C_{12}), myristic acid (C_{14}), palmitic acid (C_{16}), oleic acid (C_{18}), ricinoleic acid (C_{18}), or 12-hydroxystearic acid (C_{18}).

15. A solid solution according to claim 6 wherein (b) comprises a monoester of a (C_{6-14}) fatty acid and a disaccharide.

16. A solid solution according to claim 6 wherein (b) comprises a monoester of a (C_{8-18}) fatty acid and a trisaccharide.

17. A solid solution according to any one of claims 5 to 16 wherein (b) comprises a monoester having an HLB-value of at least 10.

18. A solid solution according to any one of claims 5 to 17 wherein (b) comprises a monoester having monoester content of at least 80% by weight.

19. A solid solution according to any one of claims 5 to 18 wherein (a) comprises a substantially water insoluble pharmaceutically active compound.

20. A solid solution according to any one of claims 5 to 19 wherein (a) comprises a pharmaceutically active polypeptide.

21. A solid solution according to claim 20 wherein (a) comprises a substantially water insoluble pharmaceutically active polypeptide.

22. A solid solution according to claim 21 wherein (a) has a molecular weight of from 500 to 1500.

23. A solid solution according to claim 21 wherein (a) is a cyclosporin.

24. A solid solution according to claim 23 wherein (a) is Ciclosporine.

25. A solid solution according to claim 23 or 24 comprising up to 30% by weight of cyclosporin based on the total weight of cyclosporin plus component (b).

26. A solid solution according to claim 23 or 24 comprising at least 1% by weight of cyclosporin based on the total weight of cyclosporin plus component (b).

27. A solid solution according to any one of claims 5 to 26 wherein (b) comprises saccharose monolaurate.

28. A solid solution according to claim 27 wherein (a) comprises a cyclosporin in an amount up to 16% by weight based on the total weight of components (a) plus (b).

29. A solid solution according to any one of claims 5 to 26 wherein (b) comprises raffinose monolaurate.

30. A solid solution according to claim 29 wherein (a) comprises a cyclosporin in an amount up to 13.5% by weight based on the total weight of components (a) plus (b).

31. A process for the production of a solid solution according to any one of claims 5 to 30 which process comprises:

a) dissolving components (a) and (b) in a volatile solvent and volatilising the solvent, or

b) liquifying component (b) by melting, dissolving component (a) in the obtained melt and solidifying the obtained solution by cooling;

and recovering the obtained solid solution.

32. A pharmaceutical composition comprising a solid solution according to any one of claims 5 to 30.

33. A pharmaceutical composition according to claim 32 the form of a capsule, pellet, granulate, tablet, ampoule, gel, suppository or globulus.

34. A liquid solution obtained by dissolving a solid solution according to any one of claims 5 to 30 in an aqueous medium or in a solvent miscible with water.

35. A liquid solution comprising a substantially water insoluble pharmaceutically active polypeptide in solution in an aqueous medium or in a solvent which is miscible with water, together with a water soluble monoester of a saturated or unsaturated (C_{6-18}) fatty acid and a polyol.

36. A solution according to claim 34 or 35, comprising at least 0.35% by weight of a cyclosporin..

37. A solution according to claim 34 or 35 for oral, buccal, lingual, percutaneous, intracutaneous, occular, cutaneous, vaginal, rectal or parenteral administration.

38. A solution according to claims 34 or 35 for intravenous administration.

39. A pharmaceutical composition, comprising a mixture according to claim 3 and optionally a substantially water insoluble excipient.

40. A pharmaceutical composition, comprising a liquid solution according to claim 34 or 35.

41. Pharmaceutical composition according to any one of claims 4 or 40 comprising a cyclosporin as active ingredient for use as an immunosuppressive, anti-inflammatory or anti-parasitic agent.

42. A method for the administration of a pharmaceutically active agent to a subject in need thereof, which method comprises administering t said subject an effective amount of a pharmaceutical composition accordingly to any one of claims 4, 39 or 40.

43. A method of effecting immunosuppression or for the treatment or inhibition of inflammatory conditions or diseases or parasitic infections or attacks in a subject in need thereof, which method comprises administering to said subject an effective amount of a pharmaceutical composition according to any one of claims 4, 39 or 40.

44. A solid solution according to any one of claims 5 to 30 or liquid solution according to claim 34 or 35 for use as a pharmaceutical.

45. A liquid solution according to claim 44 for use as a pharmaceutical by intravenous administration.